Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

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Triticonazole

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration under Section 17 of the Pest Control Products (PCP) Regulations for the active ingredient triticonazole and the formulated product Charter Seed Treatment®.

This regulatory note provides a summary of the data reviewed and the rationale for the regulatory decision concerning these products.

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Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2250 Riverside Drive
A.L. 6606D1
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca/pmra-arla/
Information Service:
1-800-267-6315 or (613) 736-3799
Facsimile: (613) 736-3798

Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration under Section 17 of the Pest Control Products Regulations for the active ingredient triticonazole and the formulated product Charter Seed Treatment®. Charter® is intended for control of smuts and bunts of wheat, barley and oats.

Methods for analysis of triticonazole residues in various media can be made available to monitoring agencies and research institutions upon request to the PMRA.

Aventis CropScience Canada will be providing additional residue and environmental data as a condition of this temporary registration. Following the review of this new data, the PMRA will publish a Proposed Regulatory Decision Document (PRDD) and request comments from interested parties before proceeding with the final regulatory decision.

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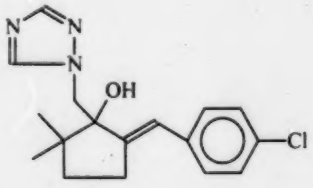
1.0 The active substance, its properties, uses, proposed classification and labelling

1.1 Active substance and preparation

Identity of the active substance and preparation containing it.

Common name:	Triticonazole
Function:	Fungicide
Chemical name:	
International Union of Pure and Applied Chemistry (IUPAC):	(±)(E)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol
Chemical Abstract Services (CAS):	5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol
CAS number:	131983-72-7
Molecular formula:	$C_{17}H_{20}ClN_3O$
Molecular weight:	317.82
Structural formula:	
Nominal purity of active:	92.5%
Identity of relevant impurities of toxicological, environmental and/or other significance:	Technical grade triticonazole does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track-1 substances

1.2 Physical and chemical properties of active substance

Table 1.1 Technical product

Property	Result	Comment
Colour and physical state	White to creamy powder	
Odour	None	
Melting point/range	140°C; PAI displays two crystalline forms melting at 137°C and 141°C	
Boiling point/range	PAI decomposes, beginning at 180°C	
Density	1.343 g/mL	
Vapour pressure	$<0.1 \times 10^{-5}$ Pa at 50°C	Non-volatile
Henry's law constant at 20°C	$<3.8 \times 10^{-5}$ Pa·m^{-3}·mol^{-1}	Low potential to volatilize from water and moist surfaces
Ultraviolet (UV) / visible spectrum	λ_{max} at 212 nm and 263; no absorbance above 320 nm	Indicates a low potential for phototransformation
Solubility in water at 20°C	8.4 mg/L	Low solubility and solubility is independent of pH
Solubility in organic solvents	Solvent — g/L Hexane — 0.12 Methanol — 18.2 Acetone — 74.5 Toluene — 12.6 2-Propanol — 7.6 Dichloromethane — 191.0 Ethyl acetate — 48.6 *n*-Octanol — 6.2	
n-Octanol–water partition coefficient	Log K_{ow} = 3.29 at 20°C (PAI)	Potential for bioconcentration/bioaccumulation
Dissociation constant	Does not dissociate	No dissociable functionality based on structure
Stability (temperature, metal)	Stable Known to be stable under the following conditions: 14 days at 54°C 30 days at 50°C 14 days in strong light 1 year ambient conditions 2 years in dark	

Table 1.2 End-use product: Charter® Seed Treatment fungicide

Property	Result
Colour	Opaque dark pink
Odour	None detected
Physical state	Liquid
Formulation type	Aqueous suspension
Guarantee	Triticonazole: 25 g/L (nominal)
Container material and description	Non-permeable polyethylene or polyethylene lined metal is anticipated; sizes 1, 4, 10, 100 and 1000 L
Specific gravity	1.069 g/mL
pH	7.63
Oxidizing or reducing action	No reaction with water, hexane, monoammonium phosphate or zinc; mild reaction with potassium permanganate
Storage stability	No change after 1 year ambient or 2 years in dark
Explodability	Does not have any components or properties that are explosive

1.3 Details of uses and further information

Triticonazole is a new active ingredient in the sterol inhibitor class of fungicides. It is registered in Europe in 1993 as a cereal seed treatment, Real, but is not yet registered in the United States (U.S.). Triticonazole has upward mobility within the plant and both contact and systemic activity against pathogens.

Charter® is a fungicide seed treatment containing 25 g/L triticonazole for application to cereals to control loose smut and common bunt of wheat, loose smut of barley and loose smut and covered smut of oats. Charter® should be applied at 2.5 g active ingredient (a.i.)/100 kg seed in either commercial seed treatment plants or on-farm treating equipment. Treated seed may be stored for up to 18 months provided seed is tested for germination prior to planting.

1.4 Classification and labelling

1.4.1 Triticonazole (technical)

Technical Triticonazole is of low acute toxicity via the oral and dermal routes, was slightly acutely toxic via the inhalation route and a minimal irritant to eyes. It was not dermally irritating nor a skin sensitizer.

The proposed label should include the following statement, to adequately identify the acute inhalation hazard:

Primary Display Panel: "CAUTION POISON".
Secondary Display Panel: "Harmful if inhaled. Avoid inhaling or breathing dust."

1.4.2 Charter® (2.59% technical grade triticonazole) end-use product (EP)

Charter® was of low acute toxicity via the oral, dermal and inhalation routes, a slight irritant to skin and minimal irritant to eyes and not a skin sensitizer. None of the inert ingredients appears on the U.S. Environmental Protection Agency (EPA) lists of inerts of toxicological concern.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

A high performance liquid chromatographic (HPLC) method was used for the determination of the active substance and a (similar) HPLC method was used to determine the significant structurally related impurities (content ≥0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

An HPLC method was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy and is suitable for use as an enforcement analytical method.

2.3 Methods for residue analysis

2.3.1 Methods for residue analysis of plants and plant products

The residue of concern (ROC) was defined from the winter and spring barley and wheat metabolism studies as the parent compound, triticonazole.

2.3.1.1 Data gathering method

The analytical method developed for the quantification of triticonazole residues in cereals involves gas chromatography with a thermionic detector (GC/TID). The method limits of quantitation (LOQs) for triticonazole are 0.01 ppm on grain and 0.05 ppm on straw. The standard deviations measured with respect to recoveries following spiking at the LOQ were indicative of the method having good repeatability. Representative chromatograms of control samples showed no interferences from matrix components or from reagents, solvents and glassware.

	Matrix		
	Barley grain	**Barley straw**	**Wheat straw**
LOQ	0.01 ppm	0.05 ppm	0.05 ppm
Mean recovery (%) ± SD	109±10 (n = 6)	103±18 (n = 6)	86±11 (n = 5)

A GC/MS analytical method was developed to analyse residues of triticonazole and its hydroxy metabolites (RPA 406341, RPA 404886 and RPA 406780) in cereal straw and green plant. The method limit of detection and limit of quantitation for each analyte have been estimated at 0.01 and 0.06 ppm, respectively. The response of the mass selective detector appeared to be linear over the range of 0–1 μg/mL (correlation coefficient not provided) but non-linear over the range of 1–10 μg/mL. The method validation indicated the following values:

	Mean recovery (%) from green plant material			
Spiking level (ppm)	**Triticonazole**	**RPA 406341**	**RPA 406780**	**RPA 404886**
0.04	27	61	98	70
0.08	44	82	101	99
0.2	23	61	86	175
Mean ± SD	31±11 (n = 3)	68±12 (n = 3)	95±8 (n = 3)	114±54 (n = 3)

Low recoveries of triticonazole were a result of apparent losses due to early elution in the solid-phase extraction cleanup procedure, which was established to be because of aqueous-containing residual acetone. Neither of these methods was validated through an independent laboratory, therefore, the submission of interlaboratory validations, to demonstrate the reproducibility of the GC/TID and GC/MS analytical methods, are required for full registration.

2.3.2 Methods for residue analysis of food of animal origin

The ROC was defined from the dairy cattle and poultry metabolism studies as the parent compound, triticonazole.

A GC/ECD analytical method was developed to determine residues of triticonazole in beef and poultry tissues, fat, milk and eggs. The limits of quantitation are 0.01 ppm for milk and 0.05 ppm for eggs, beef and poultry tissue and fat. The detector response was found to be linear for all animal matrices. Method validation indicated that when whole milk, whole eggs, beef and poultry tissue and fat are spiked at LOQ and 5× LOQ, recoveries were good, ranging from 75 to 109%. Representative chromatograms of control and spiked samples of beef and poultry tissues, eggs and milk showed no

background interferences from matrix coextractives, glassware or reagents. The method appeared to have good repeatability and specificity. This method was not validated through an independent laboratory, therefore, the submission of an interlaboratory validation for this GC/ECD analytical method is required for full registration.

	Matrix				
	Milk	**Eggs**	**Beef tissue**	**Poultry tissue**	**Fat**
LOQ	0.01	0.05	0.05	0.05	0.05
Mean recovery (%) ± SD	91±6 (n = 6)	85±10 (n = 6)	97±6 (n = 6)	97±8 (n = 6)	106±4 (n = 4)

3.0 Impact on human and animal health

3.1 Integrated toxicological summary (Appendix I)

Triticonazole administered orally to rats was rapidly absorbed and metabolized via hydrolysis. Elimination occurred rapidly mainly via faeces and partly via urine. Triticonazole had limited tissue accumulation where highest tissue levels occurred in liver, adrenals, fat, skin and fur. Metabolism was almost complete with only trace amounts of the parent compound recovered unchanged from the faeces. Differences in metabolism and excretion between males and females were minor and quantitative rather than qualitative in nature.

Technical triticonazole was of low acute toxicity by the oral and dermal routes and slightly acutely toxic by the inhalation route in rats, minimally irritating to rabbit eyes, not irritating to rabbit skin, and not a skin sensitizer in Guinea pigs. The major impurity of synthesis of triticonazole, identified as RPA402570, was of low acute toxicity in rats following oral and dermal exposure. The end-use formulation, Charter®, was of low acute toxicity by the oral and inhalation routes in rats and of low acute toxicity via the dermal route in rabbits. It was a minimal irritant to rabbit eyes, a slight irritant to rabbit skin and not a skin sensitizer in guinea pigs.

In subchronic and chronic dietary/oral studies conducted in mice, rats and dogs, the dog was identified as the most sensitive species with toxicity manifesting in adrenal cortical histopathology, lenticular cataracts, effects on testes and prostate weights and on clinical-chemistry parameters (cholesterol and albumin). However, in a developmental study in rabbits following exposure via gavage, significantly increased mortality was observed after 7–9 days of treatment indicating rabbits are considerably more sensitive to the toxicity of triticonazole than are dogs, rats and mice. Rats demonstrated the least sensitivity to the toxic effects of triticonazole among the four species tested. No evidence of toxicity was observed in rats following dermal exposure at the limit dose of 1000 mg/kg body weight (bw)/day.

Toxicity appeared to be cumulative in rats, where long-term exposure produced similar pathological effects but at lower dose levels. There was no definitive indication of gender sensitivity observed in all three species tested. However, following short-term dietary exposure to triticonazole in rats, males demonstrated effects on body weight, adrenal gland and liver at a lower dose level than did females.

The adrenal gland and liver were identified as the target organs in mice, rats and dogs. In rats and dogs, triticonazole caused histopathological changes in the cortex of the adrenal gland following short- and long-term exposure where as in mice, increased adrenal weights were not accompanied by any corresponding histopathology. Effects in the liver in all three species ranged from effects on weight, microsomal enzyme levels and/or histopathological changes.

Triticonazole was not genotoxic or oncogenic in mice and female rats. Thyroid adenomas were noted in male rats at high doses. However, adenomas are a benign tumor, there were no thyroid follicular cell carcinomas (malignant) observed in any animal, there were no other indications of thyroid toxicity observed in this study, only male rats were affected, there were no other treatment-related tumors observed in male or female rats or in any other species tested (mice, dogs and rabbits) and the genotoxicity studies all yielded negative results. Hence, the thyroid adenomas observed only in male rats are considered of minimal concern with respect to human health, since rodents are well known to be more sensitive physiologically to thyroid hormone perturbations than are humans.

Triticonazole also caused changes in reproductive organs in dogs, rats and mice, where effects on ovaries, testes or prostate weights unaccompanied by any corresponding histopathology were observed following short-term exposure only. Decreased uterine weights were also observed in rats and mice following short-term dietary exposure with histopathological changes observed only in the rats. No effects in reproductive organs were observed in rodents following chronic dietary exposure. However, the potential toxic effect of triticonazole on reproductive parameters of both males and females are highlighted in the rat reproduction study, where increases in ovary weights, vacuolation of ovarian cells, decreased mating and fertility indices and decreased litter size and live-birth index were observed. No age-related sensitivity was observed, as effects in the offspring (i.e., decreased viability index and pup body weight) were seen to occur only at maternally toxic doses in rats.

Triticonazole was not teratogenic in rats or rabbits. Although skeletal anomalies such as elongation of the acromion processes and supernumerary ribs occurred in rabbit and rat fetuses, no evidence of age-related sensitivity was observed as effects in the offspring occurred only at or above maternally toxic doses.

Triticonazole was not neurotoxic following long-term exposure in rats, nor were there any developmental anomalies of the nervous system noted in the developmental toxicity studies in rats and rabbits. No behavioural nor neurological effects were observed in the offspring in the two-generation reproductive toxicity study. In addition, the 13-week subchronic-neurotoxicity study in rats demonstrated no effects in the functional observation battery nor on motor activity testing.

Lenticular cataracts and degeneration of the lens were observed in all male and three of four female dogs following a one-year oral exposure. The mode of action of triticonazole is through inhibition of sterol demethylation. Thus, the apparent effect on cholesterol and on organs/tissues that are involved in steroid synthesis may be related to the inhibition of synthesis of cholesterol. One postulated mechanism contends that inhibition of HMG-CoA reductase, a target for antihyperlipidemic drugs, may produce some of the ocular effects observed in this study. However, the absence of mechanistic data as well as a lack of a structure–activity relationship between triticonazole and known HMG-CoA reductase inhibitors render impossible the determination of a definitive site of action.

A possibility exists that, at high doses, triticonazole may cause endocrine effects in mice, rats and dogs. The significant reduction in mating and fertility indices in rats noted at high doses of the F_1 parental generation may be an indication of cumulative toxicity in both sexes; this reduction may be correlated with the observation of increased ovary weights and associated vacuolation of ovarian cells in females and with perturbations of the endocrine function of the adrenal gland as evidenced by adrenal pathology in both sexes. Adrenal gland weights were decreased in F_0 and F_1 females. Histopathological examination of the adrenals in both sexes showed that adrenal effects were more severe in females. In male dogs following a one-year oral exposure of triticonazole, the toxicologically significant alterations in the testes and prostate weights combined with the histopathological effects on the adrenal cortex correlated with the decrease in serum cholesterol reported at the same dose level, which suggest an effect on steroid metabolism. Decreased uterine weights were observed in rats and mice following short-term dietary exposure and thyroid adenomas were noted in male rats following chronic exposure.

3.2 Determination of acceptable daily intake (ADI)

The recommended ADI for triticonazole is 0.008 mg/kg bw/day. The most appropriate study for selection of toxicity end points for chronic dietary exposure was the 52-week study with a no observed adverse effect level (NOAEL) of 2.5 mg/kg bw/day in dogs where target organ toxicities were observed as adrenal cortical cell vacuolation, decreased cholesterol and albumin levels, changes in testes and prostate organ weights at and above 25 mg/kg bw/day and lenticular cataracts at 25 mg/kg bw/day. An additional (3×) safety factor (in addition to the usual 100-fold for inter- and intra-species variation) was deemed necessary, due to observed effects on reproductive performance (rats), reproductive organ toxicity (dogs and rats; testes, prostate, ovary, uterus) and offspring toxicity (rats). In the absence of any evidence of age related sensitivity, a safety factor (SF) of 300-fold was applied to the NOAEL of 2.5 mg/kg bw/day as follows:

$$\text{ADI for Triticonazole} = \frac{\text{NOAEL}}{\text{SF}} = \frac{2.5}{300} = 0.008 \text{ mg/kg bw/day}$$

The ADI of 0.008 mg/kg bw/day provides a margin of safety (MOS) of:

- 6750 for reproductive performance/offspring toxicity (NOAEL = 54 mg/kg bw/day);

- 3675 for the development of thyroid follicular cell adenomas in male rats following chronic dietary exposure to triticonazole (NOAEL = 29.4 mg/kg bw/day in males);

- 3125 for lenticular cataracts in one-year dog study (NOAEL = 25 mg/kg bw/day); and

- 625 for developmental toxicity (elongated acromion process in rabbit fetuses. NOAEL = 5 mg/kg bw/day).

3.3 Acute reference dose (ARfD)

3.3.1 Acute toxicity: females (13+)

Based on the increased incidences of skeletal anomalies, i.e., elongation of the acromion process and delayed ossification of the metacarpals and phalanges (rabbit) and supernumerary ribs (rat) observed in teratogenicity studies following exposure to triticonazole (effects observed at maternally toxic doses), an ARfD was deemed necessary for the subpopulation of females (13+). The recommended ARfD is 0.017 mg/kg bw/day based on the lowest developmental NOAEL of 5 mg/kg bw/day in the rabbit teratogenicity study and utilizing an uncertainty factor of 300.

An additional (3×) safety factor (in addition to the usual 100-fold for inter- and intra-species variation) was deemed necessary, due to

- possible hormonal perturbations occurring during organogenesis and resulting in skeletal abnormalities, although no hormone assays were performed in any studies;

- occurrence of skeletal abnormalities at dose levels where only minimal maternal toxicity was observed; and

- lack of available information to determine whether or not the observed skeletal abnormalities were a transient phenomenon or whether they persisted through postnatal development into adulthood.

3.3.2 Acute toxicity: general population

In the context of the low order of acute toxicity of triticonazole following exposure by oral, dermal and inhalation routes, it is not necessary to propose an acute reference dose for the general population.

3.4 Toxicology endpoint selection

Complete and acceptable toxicology data were available for review of the new technical active ingredient, triticonazole.

- Triticonazole was of low acute toxicity in rats via the dermal route of exposure and no significant systemic toxicity was observed at a limit dose of 2000 mg/kg bw. In a short-term (23-day) dermal toxicity study in rats no evidence of toxicity was observed at the limit dose of 1000 mg/kg bw/day, where a full range of parameters were investigated including clinical signs, body weight gain, hematology and clinical chemistry, macroscopic and microscopic pathology.

- Triticonazole has been shown to be rapidly and extensively metabolized and excreted in the rat with no evidence of bioaccumulation following repeat oral exposures.

- The dose–response curve for triticonazole toxicity has been well characterized in several species (mouse, rat, dog) following subchronic and chronic oral administration. There was no definite indication of gender sensitivity.

- In subchronic and chronic oral studies, noted toxicologically significant effects were adrenal cortical histopathology in rats and dogs, altered clinical chemistry parameters (decreased cholesterol and albumin) and lenticular cataracts in dogs and liver effects in rats and mice.

- In subchronic and chronic dietary/oral studies conducted in mice, rats and dogs, the dog was identified as the most sensitive species. The rat appeared to be the least sensitive to triticonazole toxicity among all the species tested.

- Subchronic oral exposure in rats and dogs produced a similar range of effects at comparative effect levels. Chronic toxicity studies showed qualitatively similar toxicity and target organ as in the subchronic toxicity studies. However, toxicity appeared to be cumulative in rats where long-term exposure produced effects at lower dose levels. In the reproduction studies, toxicity was cumulative as more toxic effects were noted in the second generation. Triticonazole was not tumorigenic in mice or female rats and was not mutagenic or clastogenic.

- Tumorigenicity was noted in the thyroids of male rats (benign tumours) at doses ≥204 mg/kg bw/day with a NOAEL at 29.4 mg/kg bw/day. A threshold margin of exposure (MOE) approach was used. The mechanism of tumorigenicity was consistent with a non-genotoxic, mitogenic process whereby thyroid toxicity (follicular cell hypertrophy) maybe the critical determinant in the formation of thyroid follicular cell adenomas.

- Triticonazole is a reproductive toxicant at high doses with effects on reproductive performance in rats, on reproductive organs in rats and dogs, and on rat pup mortality and body weight. It was not teratogenic and no increased susceptibility

of fetuses to *in utero* exposure to triticonazole was demonstrated in the developmental toxicity studies in rats and rabbits. Triticonazole was not neurotoxic.

- Exposure of on-farm applicators and seed handlers would be of a short-term duration (i.e., 2 or 3 days to a few weeks per year) and would be predominately via the dermal route (~90–95% of exposure). As such the subchronic 23-day dermal toxicity study in rats was considered the most relevant study for toxicity endpoint selection. A full range of parameters were investigated including clinical signs, body weight gain, hematology and clinical chemistry, and macroscopic and microscopic pathology.

- Exposure of commercial seed treaters would be of an intermediate term (i.e., 1–6 months over the course of a year, with most treating occurring between February and May) and also via the dermal route (~99%). As such a longer duration than the 23-day dermal toxicity was considered appropriate since increased toxicity was observed in rats following increased duration of exposure. The one-year dog study (NOAEL = 2.5 mg/kg bw/day) was considered as the most relevant study as the dog was identified as the most sensitive species with toxicity manifesting as adrenal cortical histopathology, lenticular cataracts, effects on testes and prostate weights and on clinical chemistry parameters (cholesterol and albumin).

- A MOE of 300 is recommended to account for intraspecies (10×) and interspecies (10×) differences and an additional safety factor (3×) for reproductive performance/reproductive organ toxicity (testes, prostrate, ovary, uterus) effects and organ toxicity.

3.5 Impact on human health arising from exposure to triticonazole

3.5.1 Operator exposure assessment

Charter® is a new seed treatment fungicide for the control of various seed-borne diseases in wheat, oats and barley. It contains 25 g/L of the active ingredient triticonazole. It is proposed for use in both commercial and on-farm treating facilities. The proposed application rate for Charter® is 5 g a.i./100 kg seed (50 mg a.i./kg seed). However, as a result of the efficacy review, one half the application rate (25 mg a.i./kg seed) is being recommended. No mixing is required as Charter® is a ready-to-use product. The quantity of a.i. handled in a day depends on the amount of seed treated and will be different for commercial and on-farm facilities. The amount of seed treated will depend on the size of the facility and the seed being treated.

In commercial facilities, one to three people would generally be involved in seed treating. Typical tasks include mechanical and manual loading of chemical and seed into mixing auger, supervision of application equipment, bagging, sewing filled bags, moving bags to pallets, bulk loading treated seed to trucks or seeding equipment and cleaning seed treatment area, equipment and seed storage bins. The same person or different people

may carry out all or some of these tasks. Application is generally via a closed, calibrated metering system fed to an auger to be mixed with seed. Loading can either be open pouring or closed via hard-couple linkage. Clean-up of auger and treating equipment is performed daily and is necessary before a different type of seed is treated. Typically a Canadian commercial seed-treating facility can treat approximately 46 000 kg of seed in a day but a range of between 3000 and 200 000 kg of seed can be treated. Based on half the proposed application rate, approximately 1.2 kg a.i. will be typically handled in a day. Application at a commercial facility can be daily or based on demand for treated seed. Commercial seed treatment occurs over several months (1–6 months), with most seed being treated between February and May.

On-farm treating generally involves one person and is conducted once per year. Seed is treated as needed during sowing of crops with only the amount of seed needed for sowing the crop being treated. The seeding rate for wheat, oats and barley is approximately 110 kg seed/ha and approximately 80 ha/day of wheat can be sown. Therefore approximately 8800 kg of seed will be treated in a day resulting in 0.22 kg a.i. handled/ day assuming an application rate of 25 mg a.i./kg seed. Less hectares per day would be sown with oats and barley resulting in less a.i. handled per day. Typically on-farm treatment would be done over a few days to a few weeks in spring just prior to or during seeding the fields. On the farm, seed may be treated and planted by a variety of methods including gravity flow or mist-type seed treatment equipment or using a treat-on-the-go a.i.r seeder. In rare instances, some small operations may mix manually with a paddle in a barrel or hopper. Exposure may occur while loading the product, while handling treated seed (e.g., levelling the seed in small hoppers) or during equipment cleaning and maintenance.

Dermal absorption data was provided to estimate potential dermal penetration of triticonazole. Male Sprague-Dawley rats were administered nominal doses of 0.15 and 3.0 mg/cm^2 of ^{14}C-triticonazole and monitored up to 72 h post-dosing. Four animals were treated for each group at each dose level, and sacrifices were made at 8, 24 and 72 h after application of the dose. The skin site of all animals was washed after 8 h. Mean dermal absorption values were 56.38 % absorption after 8 h; 41.97% after 24 h; and 35.84% after 72 h at the low dose, and 14.79% absorption after 8 h; 7.41% after 24 h; and 9.81% after 72 h at the high dose. The 24-h low dose absorption rate of 42% is recommended for this use scenario, as exposure is expected to be daily when it occurs, and a wash was conducted at 8 h post-dosing, which would simulate showering after the workday.

A commercial seed treatment passive-dosimetry study was submitted as a surrogate to estimate exposure when treating seeds at a commercial facility. The study was conducted using two formulations of carbathiin: Vitaflo-280, and Vitavax Single, both of which are currently registered for seed treatment use in Canada. The study was conducted at two Canadian sites: a seed treatment and bagging facility in using Vitaflo-280 formulation, and a bulk seed treatment facility using Vitavax Single formulation. The varieties of seed treated during the monitoring periods included wheat, barley, oats and peas. Seed was treated at the recommended rates for Vitavax and Vitaflo formulations (613 and 417 mg a.i./kg seed, respectively), rates much higher (8–12 times) than that proposed for Charter® (50 mg a.i./kg seed). Results showed overall mean exposures (dermal +

inhalation) from both sites of 1514.6 μg/kg a.i. (SD 2981.2). The very large standard deviations demonstrate the large differences in exposure potential in seed treatment facilities. Hands received approximately 86% of the total dermal exposure, whereas inhalation accounted for only 1% of total exposure. Workers receiving the highest exposures were those who were in direct contact with the treated seed, either during clean up, or from entering storage or transfer areas containing treated seed. Study limitations included the small number of individuals monitored at each site, and the problems observed with the field recovery results.

Using the μg/kg a.i. values from the surrogate study and the amount of triticonazole handled/day, the extrapolated estimate of exposure to triticonazole was 1.76 (range 0.24–10.06) mg/day. Assuming a 70-kg person the potential exposure is 0.025 mg/kg bw/day. Factoring in the dermal absorption value of 42%, the daily absorbed dose to triticonazole when treating seed in a commercial facility is 0.01 mg/kg bw/day.

A Pesticide Handlers Exposure Database (PHED) 1.1 assessment was submitted to quantify exposure to triticonazole when conducting on-farm seed treatment with Charter®. The PHED is a database of generic mixer/loader/applicator passive dosimetry data which facilitates the generation of scenario specific exposure estimates. This PHED assessment conforms to the North American Free Trade Agreement Guidelines for using and reporting PHED data. The PHED subsets compare well to the proposed formulation and use pattern and is therefore acceptable as surrogate data for estimating exposure to triticonazole for on-farm seed treatment. The PHED estimate is based on a worker wearing one layer of clothes (e.g., long-sleeve shirt, pants) and gloves while mixing and loading Charter®. The personal protective equipment (PPE) recommended on the label is coveralls and gloves for workers handling Charter® or treated seed. Since application to seed is done using a calibrated metering system and is largely closed, application exposure is expected to be negligible. Based on this data, a potential exposure of 0.15 μg a.i./kg bw/day was estimated for a 70-kg farmer loading 0.22 kg/day of triticonazole to treat 8800 kg of wheat seed using closed application equipment. Factoring in the dermal absorption value of 42%, the absorbed dose is 0.07 μg a.i./kg bw/day. The primary route of exposure was dermal, only 4.5% was by inhalation. Based on a qualitative assessment, there will be some additional exposure from other activities related to the seeding operation, but this exposure is likely to be less than that associated with handling and pouring Charter®. Exposure for treating other cereal seeds (i.e., barley and oats) would be the same or less, as less seed would be treated.

The triticonazole exposure values and MOEs for commercial seed treaters and on-farm seed treaters are presented in Table 3.1. All exposure estimates are based on wearing one layer of clothing and wearing gloves when appropriate.

The MOE for on-farm applicators is greater then 5×10^6 and is considered adequate. The 23-day dermal rat study with a NOAEL of 1000 mg/kg bw was used for the risk assessment for these exposure scenarios, because it had a relevant duration and route of exposure. However, the rat is also the least sensitive species. It was felt though, that MOEs greater than 1000 would be protective even though the least sensitive species (rat) was used as a model for toxicity.

The MOE for commercial treaters was 250. An MOE of 300 is targeted due to reproductive toxicity. The 23-day dermal rat study used for the on-farm treater and seed-handler risk assessment was felt to be of too short a duration for this exposure scenario. Therefore, the toxicological study selected for the risk assessment for this exposure scenario was the one-year dog study with a NOAEL of 2.5 mg/kg bw and from which the MOE of 250 was derived. In the absence of a dermal study with an appropriate duration of exposure, the dog study was selected, because the dog was identified as the most sensitive species. However, this study reflects a conservative NOAEL for risk assessment, given that the compound is administered to the dogs orally by capsule for a one-year period, which is a substantially different exposure scenario from the dermal route of exposure to which commercial seed treaters would be subjected. The lowest observed adverse effect level (LOAEL) for dog study was 25 mg/kg bw based on adrenal cortical histopathology and changes in clinical chemistry parameters. Realistically, the MOE using the LOAEL from the one-year dog study would lie in the range of 250–2500. Since an oral NOAEL was used in the risk assessment, the exposure estimate factored in a dermal absorption value of 42%. This value is conservative, since a large portion of the dermal exposure to triticonazole may be due to treated seed dust and dermal absorption of triticonazole adhered to dust is expected to be lower than that obtained in the dermal absorption study. Therefore the MOE of 250 is considered adequate.

3.5.2 Bystanders

Given the proposed commercial and agricultural use scenarios, exposure and risk to bystanders should be minimal.

3.5.3 Post-application exposure

Post-application exposure can occur as a result of handling treated seed. Treated seed to be sown in fields is added to hoppers on the seeders either manually (smaller bags of treated seed) or mechanically with augers and forklifts (large bags of treated seed or bulk seed containers). The largest potential for exposure from handling treated seed is during the loading of seed into the seeder hoppers and when levelling the treated seed in the hopper by hand. Once in the hopper, there is little contact with treated seed. Typically sowing of fields would occur for a few days to a few weeks in the spring and would depend on the crop and size of field to be seeded. Therefore, post-application exposure to triticonazole from handling treated seed would only occur for a few days to a few weeks each year. The seeding rate for wheat, oats and barley is 110 kg seed/ha and approximately 80 ha/day of wheat can be sown. Therefore approximately 8800 kg of seed will be sown in a day resulting in approximately 0.22 kg a.i. being handled indirectly in a day, assuming an application rate of 25 mg a.i./kg seed. Less hectares per day would be sown with oats and barley resulting in less a.i. handled per day.

Two surrogate passive dosimetry studies were submitted to estimate exposure to triticonazole when sowing fields with seed treated with Charter®. One study, conducted in France, used winter wheat seed treated with a test product containing a marker for exposure. The estimated potential exposure for triticonazole for workers handling treated seed when sowing fields is 0.13 mg/kg bw/day. This is based on a 70-kg worker handling

8800 kg of seed treated with triticonazole at a rate of 25 mg a.i./kg seed. Factoring in a dermal absorption value of 42% the absorbed dose is 0.06 mg/kg bw/day. The hands accounted for 91% of the potential exposure, while inhalation accounted for only 1%. The triticonazole exposure estimate was extrapolated from a surrogate exposure value of 42.29 mg/kg a.i. handled. The study limitations included a low number of replicates, low number of QA/QC samples, and limited information on the formulation used in the study.

Another surrogate study to estimate exposure to triticonazole when sowing fields with treated seed was also submitted. This study was conducted in the United Kingdom in October 1993 and was reviewed previously. Baytan treated seed was used and triadimenol was the active ingredient monitored in this study. The normalized exposure derived from this study was 12.8 mg a.i./kg a.i. handled. This gives an extrapolated potential exposure estimate for triticonazole of 0.04 mg a.i./kg bw/day based on a 70-kg worker handling 8800 kg of seed treated with triticonazole at a rate of 25 mg a.i./kg seed. Factoring in a dermal absorption value of 42% the absorbed dose is 0.02 mg/kg bw/day. Dermal exposure accounted for 98% of the total potential exposure.

Despite some limitations, the two studies were collectively considered adequate to estimate potential exposure. In averaging the two exposure values for handling treated seed, we get a potential exposure of 0.09 mg/kg bw/day and an absorbed dose of 0.04 mg/kg bw/day.

The triticonazole exposure value and MOE for treated seed handlers are presented in Table 3.1. The exposure estimate is based on wearing one layer of clothing and wearing gloves when appropriate. The MOE seed handlers is greater then 11 000 and is considered adequate. The 23-day dermal rat study with a NOAEL of 1000 mg/kg bw was used for the risk assessment for these exposure scenarios because it had a relevant duration and route of exposure. However, the rat is also the least sensitive species. It was concluded that MOEs greater than 1000 would be protective even though the least sensitive species (rat) was used as a model for toxicity.

Table 3.1 Exposure estimates and resulting MOEs

Exposure scenario	NOAEL (mg/kg bw/day)	Exposure (mg/kg bw/day)	MOE
Commercial treatment	2.5	0.01	250
On-farm treatment	1000	0.0002	5×10^6
Handling treated seed	1000	0.09	11 000

The MOE for triticonazole are acceptable for commercial and on-farm applicators and seed handlers for an application rate of 25 mg a.i./kg seed or less. It should be noted however, that should the application rate be increased, an additional 90-day dermal toxicology study in rabbits will be required to further refine the risk assessment for commercial seed treaters, as the MOE would be unacceptable for this use due to higher

exposure. The following personal protective equipment should be included on the Charter® label:

- "Wear chemical-resistant gloves and chemical-resistant coveralls made of laminated, non-woven or composite fabric."

- "Wear a NIOSH-approved dust filtering respirator during clean-up activities, handling Charter® or if working area is not well ventilated."

4.0 Integrated food residue chemistry summary (Appendix II)

The plant metabolism studies appeared to indicate that ^{14}C-triticonazole was rapidly metabolized through to various hydroxylated compounds, which appeared to be subsequently incorporated into other naturally occurring products.

The confined crop rotation study indicated that residues of triticonazole were very low (<0.05 ppm) in all fractions of the rotational crops (radish, leaf lettuce and wheat) planted in soil that had been treated with triticonazole at the rate of 285.9 g a.i./ha and aged for one month, five months and one year. Therefore, it appears unlikely that residues of triticonazole and its related metabolites in soil will translocate and bioaccumulate in the rotational crops.

In the freezer storage stability study, control samples of maize grain, winter wheat grain and winter wheat straw were spiked with triticonazole at 0.01, 0.01 and 0.05 ppm, respectively, and stored at –20°C for 0, 3, 6 and 12 months. The data indicated that residues of triticonazole were stable for 12 months.

The dairy cattle and poultry metabolism studies indicated that, following oral dosing, ^{14}C-triticonazole was fairly well and rapidly absorbed and eliminated (mainly via faeces) with minimal accumulation in tissues, milk and eggs. Triticonazole appeared to be rapidly metabolized through to various hydroxylated compounds, which appeared to be subsequently incorporated into other naturally occurring products. These livestock metabolism studies were adequate for this seed (cereals) treatment petition.

No freezer storage stability information for animal matrices was submitted with this application.

According to the supervised residue trials, residues of triticonazole in livestock feed items (forage, hay and straw) ranged from 0.1 to 0.2 ppm when seeds are treated according to the proposed Canadian use pattern. Based on the maximum anticipated theoretical dietary burdens of triticonazole to poultry, beef and dairy cattle and the absence of quantifiable residues of triticonazole or any compound of toxicological interest in eggs, milk, meat and meat by-products, as demonstrated in the poultry and dairy cow metabolism studies, a MRL of 0.01 ppm for milk and 0.05 ppm for eggs, meat and meat by-products of poultry, cattle, horses, hogs, goats and sheep, should be established to cover potential residues of triticonazole.

The results from Canadian supervised field trials demonstrated that residues of triticonazole in cereal (wheat, barley and oats) grains did not exceed the method LOQ (0.01 ppm) when seeds were treated with a flowable formulation of triticonazole at rates ranging from 10 to 35 g a.i./100 kg seed (4–14× Canadian gap) and harvested 77–116 days following emergence. Therefore, a MRL of 0.01 ppm should be established to cover residues of triticonazole on cereal (wheat, barley and oat) grains.

As triticonazole is to be applied as a seed treatment, no residue decline studies were required. Because residues of triticonazole were below the LOQ (<0.01 ppm) on cereal grains treated at 14× the proposed Canadian application rate, a processing study was not required.

For the chronic dietary risk assessment, the PDI accounted for 3 and 7% of the acceptable daily intake (ADI = 0.008 mg/kg bw/day) for the total population and children 1–6 years, respectively. The acute dietary risk assessment, conducted for females of child-bearing age (female 13+, pregnant/nursing), indicated that the PDI accounted for 2% (95th percentile) of the ARfD (ARfD = 0.017 mg/kg bw/day).

Consequently, the proposed domestic use of triticonazole on cereals (wheat, barley and oats) does not pose an unacceptable dietary (both food and water) risk to any segment of the population, including infants, children and adults.

Since this active ingredient is a new chemical, there are no existing MRLs in Canada. On the basis of the Canadian residue data, residues of triticonazole are unlikely to exceed 0.01 ppm, when cereal grains (wheat, barley and oats) are treated according to the proposed Canadian use pattern. Therefore, a MRL of 0.01 ppm should be established to cover residues of triticonazole in cereal grains (wheat, barley and oats). Residues of triticonazole which may potentially occur in milk, eggs, meat and meat by-products as a result of feeding of forage, hay, straw and grain to livestock and poultry are not expected to exceed the method LOQ of 0.01 ppm for milk and 0.05 ppm for all other animal matrices. Consequently, MRLs of 0.01 ppm for milk and 0.05 ppm for eggs, meat and meat by-products of poultry, cattle, horses, hogs, goats and sheep should be established to cover potential residues of triticonazole. The submission of an interlaboratory validation for both the GC/TID and GC/MS analytical methods and a freezer storage stability study using animal matrices are required for full registration of triticonazole and Charter®.

Currently, no U.S. tolerances or Codex CXLs are established for residues of triticonazole in/on plant or animal commodities.

5.0 Fate and behaviour in the environment

5.1 Summary of the fate and behaviour of triticonazole in the environment

5.1.1 Transformation

Hydrolysis and photolysis are not important pathways of transformation of triticonazole in the environment. Dissipation of this product in the environment is primarily dependent upon biotransformation, which proceeds slowly. Therefore, triticonazole is relatively stable in the environment under normal conditions (Appendix III, Table 1).

5.1.2 Mobility

As determined in adsorption/desorption and soil column leaching studies, the potential mobility of triticonazole is low to moderate. The laboratory studies, however, indicated that triticonazole and its transformation products have a high leaching potential in coarse-textured and sandy soils (Appendix III, Table 1). Aged residues bind more strongly to soil, resulting in higher concentrations in the top soil layers and lower concentrations in the deeper layers and leachate. The transformation products are more polar and more mobile than the parent; therefore, they were detected in the leachate. Based on these results, there is a relatively high probability that triticonazole residues will contaminate groundwater when applied in the field under certain conditions (i.e., sandy soil). The high potential for triticonazole mobility was confirmed by the results of several screening models (Cohen et al. (1984) criteria, Groundwater Ubiquity Score (GUS) assessment method of Gustafson (1989), and Expert system for Pesticide Regulatory Evaluation and Simulation [EXPRES]). The proposed low application rate (4 g a.i./ha), however, is expected to reduce possible impact of leaching. Also the binding of residues to soil increases with time after application, thus limiting leaching over time. Therefore, leaching is not of concern for this seed treatment formulation.

5.1.3 Transformation products

Four major transformation products were detected in aerobic soils (Appendix III, Table 2). RPA 406341 was the most common transformation product and was identified as an isomer of triticonazole. The half-lives for the major transformation products were not determined. The concentration of the three of these transformation products, however, increased with time indicating they are more persistent than the parent. Based on relative persistence, polarity and a mobility study, it can be concluded that some of the transformation products are more likely to leach than the parent.

5.2 Expected environmental concentrations (EEC)

5.2.1 Soil

The EEC of triticonazole in soil was calculated to be 0.002 mg a.i./kg dry soil immediately after application, assuming a soil bulk density of 1.5 g/cm^3, a soil depth of

15 cm, and a scenario in which the maximum Canadian label rate of 4 g a.i./ha is applied once to bare soil.

5.2.2 Surface water

Under the proposed use pattern (treated seed incorporated into soil), there is little potential for exposure of surface water through surface runoff, spray drift, or accidental overspray. Therefore, EECs in water and surface runoff were not used for environmental risk assessment.

6.0 Effects on non-target species

6.1 Terrestrial organisms

Triticonazole is practically non-toxic to the birds and small wild mammals on an acute oral and short-term dietary basis. Terrestrial toxicity endpoints are summarized in Appendix III, Table 3.

6.2 Environmental risk assessment

Wild birds and mammals could be exposed to triticonazole residues as a result of consumption of contaminated seeds. The diets of bobwhite quail and the mallard duck consist of 55 and 70% seeds, respectively (Urban and Cook 1986). The diet of small wild mammals, represented by the rat and the mouse, consists of 20–50% seeds (Urban and Cook 1986). Using the maximum triticonazole application rate of 25 mg a.i./kg seed (EEC), the estimated ingestion of triticonazole via contaminated seeds is 13.8, 17.5, 5.0 and 12.5 mg a.i./kg dw diet for bobwhite quail, mallard duck, rat and mouse, respectively.

Comparison of toxicity endpoints with the EEC in the diet indicated that triticonazole, used as a seed treatment, poses a low risk to wild birds and wild mammals on an acute, dietary, chronic and reproductive basis (Table 6.1).

NOTE A confirmatory reproduction study with mallard duck is requested to support the results obtained for bobwhite quail.

Table 6.1 Summary of risk assessment to terrestrial organisms

Organism	Effect	NOEC/NOEL (mg a.i./kg diet/bw)	EEC (mg a.i./kg dw diet)	MOS	Risk	Mitigative measures
Bobwhite quail	Acute oral	2000	13.8	nd	No risk	Not required
	Dietary	1300		94		
	Reproduction	250		18		
Mallard duck	Acute oral	1000	17.5	nd	No risk	Not required
	Dietary	1300		74		

Organism	Effect	NOEC/NOEL (mg a.i./kg diet/bw)	EEC (mg a.i./kg dw diet)	MOS	Risk	Mitigative measures
Rat	Acute oral/dermal	200	5.0	nd	No risk	Not required
Rat	Dietary	250	5.0	50		
Mouse	Chronic	150	12.5	12		

nd: not determined

- The log K_{ow} of 3.29 for triticonazole (Table 1.2) triggers the need for a study of bioconcentration/bioaccumulation.

- Triticonazole is persistent in aerobic soils under laboratory conditions (DT_{50} = 145–554 days). The fate of triticonazole and its transformation products under Canadian field conditions is not known.

- Although the higher polarity of the transformation products relative to the parent indicates that they would be unlikely to bioaccumulate, their relatively greater persistence (meets TSMP criterion) triggers a confirmatory log K_{ow} for these persistent transformation products.

6.3 Mitigative measures

The recommended modifications to the label should reduce the potential exposure to non-target organisms and the contamination of water.

"Ensure proper soil incorporation of the seeds. DO NOT feed treated seed to, or otherwise expose, wildlife or domestic birds. If treated seed is spilled outdoors or in areas accessible to birds, promptly clean up or bury to prevent ingestion. Ensure proper disposal of surplus treated seed not intended for later planting. DO NOT contaminate domestic or irrigation water supplies, lakes, streams, ponds or any other body of water with the chemical, used containers, treated seed or bags which have held treated seed."

6.4 Outstanding environmental data requirements

Physicochemical properties
The log K_{ow} for the major persistent triticonazole transformation products

Canadian terrestrial field studies
Study report on the fate of triticonazole and its major transformation products under Canadian field conditions

Study report on bioconcentration/bioaccumulation (typically done with fish), triggered by log K_{ow} of 3.29

Avian reproduction study: mallard duck
Since this submission was received, the Agency has harmonized its data requirements for seed treatment in the area of avian reproduction with the U.S. EPA (i.e., requires an upland gamebird and a waterfowl study). Therefore, an avian reproduction study with mallard duck is being requested to confirm results obtained with the bobwhite quail. The reproductive risks to birds have been found acceptable for the period of the registration based on the bobwhite quail study.

6.5 References

Cohen, S.Z., Creeger, S.M., Carsel, R.F. and Enfield, C.G. 1984. Potential pesticide contamination of groundwater from agricultural uses. In: (Kruegar, R.F. and J.N. Seiber, eds.) Treatment and disposal of pesticide wastes. American Chemical Society Symposium Series No. 259. American Chemical Society, Washington, DC, pp. 297–325.

Gustafson, D.I. 1989. Groundwater ubiquity score: a simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry 8:339–357.

Urban, D.J., and Cook, N. J. 1986. Hazard Evaluation Division Standard Evaluation Procedure, Ecological Risk Assessment. U. S. EPA 540/9-85-001.

7.0 Efficacy summary

7.1 Effectiveness against smuts and bunts of wheat, barley and oats

Charter® Seed Treatment is proposed for application at 5 g a.i. per 100 kg seed to control common bunt (*Tilletia caries*) and loose smut (*Ustilago tritici*) of wheat, loose smut of barley (*Ustilago nuda)* and covered smut (*Ustilago kolleri*) and loose smut (*Ustilago avenae*) of oats.

A total of 32 efficacy trial and 24 crop tolerance trial reports were submitted in support of these claims, all from Canadian sites. Charter® was applied to seed at full and half rates and was compared with commercial standard treatments containing tebuconazole or carbathiin. Charter® was effective in controlling wheat common bunt and loose smut resulting in means of 93 and 96% control, respectively. It also reduced barley loose smut, providing 80% control, and 100% control of oat loose smut and covered smut. This performance was typically better than the commercial standards in these tests.

In comparative trials, there was typically no significant difference between the efficacy of the proposed rate (5 g a.i./100 kg seed) and half-rate (2.5 g a.i.) of triticonazole; therefore, the 2.5 g rate is considered adequate for seed treatment of smuts and bunts. Neither these rates nor higher amounts of triticonazole (up to 36× proposed rate) resulted in observable phytotoxic effect on any of the 12 cereal varieties tested.

7.2 Development of fungicide resistance

Triticonazole is chemically related to, and has the same mode of action as, triazole fungicides, which have become available for use in Canada (triadimenol, tebuconazole, difenoconazole, propiconazole). The PMRA has recently introduced a voluntary resistance-management labelling scheme based on grouping fungicides by target site and mode of action. Regulatory Directive 99-03 provides standard label statements to assist growers in deferring development of resistance to new and existing products. It is intended that these will be adopted consistently by industry in the near future. In the case of triticonazole, a general statement to alternate triazole-based products with fungicides having a different site of action is recommended for the Charter® label, with a view to revising this to the standard statements in the near future.

7.3 Conclusion

Triticonazole represents one of several alternative fungicides for Canadian cereal seed, which has traditionally been treated primarily with carbathiin and thiram. Charter® therefore offers another option for growers and is effective against smuts and bunts at a half the proposed rate of activity (2.5 g a.i./100 kg seed) compared with some older products.

As part of the value assessment, consideration was given to tolerances for triticonazole in the U.S., which would be a significant export market for Canadian grain. At the time of writing, import tolerances for the proposed use of triticonazole on wheat, barley and oats had not yet been established in the U.S. Therefore, a statement to alert growers to this situation is recommended for the Charter® label.

8.0 Overall conclusions

Charter® is a fungicide seed treatment containing 25 g/L triticonazole for application to cereals to control loose smut and common bunt of wheat, loose smut of barley and loose smut and covered smut of oats. Charter® is effective against smuts and bunts at half the proposed rates (5.0 g a.i./100 kg seed) of active ingredient. Charter® should be applied at 2.5 g a.i./100 kg seed in either commercial seed treatment plants or on-farm treating equipment. Label statements on resistance management and on U.S. tolerances are recommended. Charter® has merit and value in providing an effective fungicide option for control of the above cereal diseases.

Technical triticonazole poses a slight acute toxicity hazard by the inhalation route. No significant acute hazard is associated with the oral or dermal routes of exposure. The EP (Charter® Seed Treatment) has a slight skin and minimal eye irritation potential. Label statements (below) are recommended to identify and alleviate these hazards.

In mammals, triticonazole was shown to be well absorbed, completely metabolized and rapidly eliminated and is not considered to be neurotoxic, genotoxic, oncogenic nor teratogenic. In long-term studies, and at high doses, it appears to have effects on the

reproductive system. The target organs of toxicity following oral administration were identified as the adrenal gland, liver and reproductive organs in mice, rats and dogs.

For occupational/bystander exposures to triticonazole, the most appropriate studies for risk assessment were identified as the 23-day dermal toxicity study in rats and a one-year study in dogs.

For dietary exposure to food residues, the ADI was based on a one-year study in dogs. An additional (3×) safety factor (beyond the usual 100-fold for inter- and intra-species variation) was deemed necessary, due to observed reproductive organ toxicity (testes, prostrate, ovary, uterus), effects on reproductive performance and offspring toxicity. The recommended ADI for triticonazole is 0.008 mg/kg bw/day.

The MOE for triticonazole are acceptable for commercial and on-farm applicators and seed handlers for an application rate of 25 mg a.i./kg seed or less, provided recommended personal protective clothing are used.

In plants, ^{14}C-triticonazole was rapidly metabolized through to various hydroxylated compounds, which may have subsequently been incorporated into naturally occurring plant products.

Uptake of triticonazole and any triticonazole-related metabolites into the raw agricultural commodities (RAC) of rotational crops was low and appeared to decline with time, when soil was treated at an exaggerate rate with radiolabelled triticonazole prior to planting. Therefore, based on the confined crop rotational study, the application of triticonazole at the proposed seed dressing rate would result in minimal uptake in secondary crops.

Following oral dosing to dairy cattle and hen, ^{14}C-triticonazole was fairly well and rapidly absorbed and eliminated (mainly via faeces), with minimal accumulation in tissues, milk and eggs. These livestock metabolism studies were adequate for this seed (cereals) treatment petition.

The ROC was defined from the plant and animal metabolism studies as the parent compound, triticonazole.

A GC/TID method, developed to analyse triticonazole residues in cereal grain and straw, a GC/MS method, developed to analyse residues of triticonazole and its hydroxy metabolites in cereal straw and green plant and a GC/ECD method, developed to analyse residues of triticonazole in beef and poultry tissues, fat, milk and eggs, all demonstrated good repeatability, specificity and selectivity. However, neither of these methods was validated through an independent laboratory. Therefore, the submission of an interlaboratory validation for all three analytical methods are required for full registration.

The freezer storage stability study indicated that triticonazole residues in maize and winter wheat grain and winter straw were stable for up to 12 months when stored at –20°C. No freezer storage stability information for animal matrices was available. To

grant full registration of triticonazole and Charter®, the registrant will need to submit a freezer storage stability study for animal tissues.

The supervised field trials showed that residues of triticonazole in cereal (wheat, barley and oats) grains did not exceed the method LOQ (0.01 ppm) when seeds were treated with a flowable formulation of triticonazole at rates ranging from 4 to 14× the proposed Canadian use pattern. Therefore, a MRL of 0.01 ppm should be promulgated to cover residues of triticonazole on cereal (wheat, barley and oat) grains.

Residues of triticonazole which may potentially occur in milk, eggs, meat and meat by-products as a result of feeding of forage, hay, straw and grain to livestock and poultry are not expected to exceed the method LOQ of 0.01 ppm for milk and 0.05 ppm for all other animal matrices. Consequently, MRLs of 0.01 ppm and 0.05 ppm, respectively, should be established.

The chronic and acute dietary risk assessments demonstrated that the proposed domestic use of triticonazole as a seed treatment for cereals (wheat, barley and oats) does not pose an unacceptable dietary (both food and water) risk to any segment of the population, including infants, children and adults.

Triticonazole was not susceptible to hydrolysis or photolysis but is dissipated primarily by biotransformation, which proceeds slowly. Triticonazole is therefore relatively persistent in the environment under normal conditions. Four major transformation products were detected in aerobic soils and data suggest that these would be persistent but may not be bioaccumulative based on their polarity. Laboratory studies suggest that the active and these compounds would be mobile in coarse-textured and sandy soils; however, the low application rate and potential binding of residues to soil over time reduces concern with leaching for the seed treatment use pattern. Canadian field data on the fate of triticonazole and its transformation products, as well as additional K_{ow} figures for persistent transformation products are being requested to confirm the properties of this active and its major transformation products. A bioconcentration/bioaccumulation study is also being requested to confirm that triticonazole does not bioaccumulate.

Comparison of toxicity endpoints with the EEC in the diet indicated that triticonazole, used as a seed treatment, poses a low risk to wild birds and wild mammals on an acute, dietary, chronic and reproductive basis. A confirmatory reproduction study with mallard duck is requested to support the results obtained for bobwhite quail.

Exposure of surface water and aquatic organisms to triticonazole are not pertinent to the proposed use pattern provided that treated seed is properly stored and soil-incorporated during planting, as indicated on the Charter® label.

8.1 Label amendments for Charter®

The label incorporates the following changes as a result of the review of triticonazole:

> To meet the lowest effective rate (2.5 g a.i./100 kg seed), the product application rate is changed to 100 mL/100 kg seed. The statement on control of seed rots and seedling blights is deleted.

A general statement on resistance management is added:

> "For resistance management, note that Charter® contains a triazole fungicide. Some loss of disease control may occur over time if triticonazole or other fungicides in this group are used repeatedly or consecutively in successive years on the same fields, due to development of resistant strains of pathogens. It is recommended that fungicides with a different mode of action be alternated in the disease control program. Contact your local extension agent or crop advisor for further information on resistance management in your area."

To adequately identify the acute inhalation hazard:

> Primary Display Panel: "CAUTION POISON".
> Secondary Display Panel: "Harmful if inhaled. Avoid inhaling or breathing dust"

Under the PRECAUTIONS section of the Charter® label:

> revised to include "chemical resistant gloves", "chemical resistant coveralls made of laminated, non-woven or composite fabric" and "Wear a NIOSH approved dust filtering respirator during clean-up activities, handling Charter® or if working area is not well ventilated."

To reduce the potential exposure to non-target organisms and the contamination of water:

> "Ensure proper soil incorporation of the seeds. DO NOT feed treated seed to, or otherwise expose, wildlife or domestic birds. If treated seed is spilled outdoors or in areas accessible to birds, promptly clean up or bury to prevent ingestion. Ensure proper disposal of any surplus treated seed not intended for later planting. DO NOT contaminate domestic or irrigation water supplies, lakes, streams, ponds or any other body of water with the chemical, used containers, treated seed or bags which have held treated seed."

To alert growers to the situation with respect to U.S. tolerances, the following statement has been added:

> This is not yet a registered use pattern in the U.S. and no import tolerance has yet been established in the U.S.

8.2 Toxic Substances Management Policy considerations

During the review of triticonazole, PMRA has taken into account the federal Toxic Substances Management Policy and has followed Regulatory Directive DIR99-03. It has been determined that the product does not meet all criteria for a TSMP Track 1.

Triticonazole is persistent, according to TSMP criteria, having a half-life in aerobic soil of 145–554 days in laboratory studies, which exceeds the Track 1 cut-off criterion for soil of ≥ 182 days. Studies on the fate of triticonazole and transformation products in the field are required as a condition of this temporary registration to further refine the understanding of the fate of this product under the proposed use.

Triticonazole studies show the octanol–water partition coefficient (log K_{ow}) to be 3.29, which is below the TSMP Track 1 cut-off criterion of ≥ 5.0. Nonetheless, a log K_{ow} of >3 typically triggers a need for a bioaccumulation study and a bioaccumulation/ bioconcentration study (typically done with fish) has been requested to confirm that triticonazole is not bioaccumulative.

Triticonazole forms persistent (TSMP) transformation products, however these are unlikely to bioaccumulate, based on their polarity. Confirmatory log K_{ow} are being requested.

Toxicity of triticonazole is described in Sections 3.0, 6.1 and the appendices. Assessment of exposure from the proposed use pattern showed that margins of safety (Sections 3.5, 6.2) were sufficient to alleviate concerns with respect to human health and environment.

Triticonazole (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The formulated product does not contain any formulants that are known to contain TSMP Track 1 substances.

As a result, PMRA does not consider triticonazole to be a Track 1 substance and does not object to the temporary registration of triticonazole while confirmatory data are being collected.

9.0 Regulatory decision

The Agency has concluded that the use of Triticonazole technical and Charter® has been granted temporary registration under Section 17 of the PCP Regulations subject to the generation of the following studies:

Interlaboratory validation for GC/TID and GC/MS analytical methods

Freezer storage stability study: animal matrices

The log K_{ow} for the major triticonazole transformation products

Study report on the fate of triticonazole and its major transformation products under Canadian field conditions

Study report on bioconcentration/bioaccumulation in fish or earthworms

Avian reproduction study: mallard duck

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
EEC	expected environmental concentration
EP	end-use product
EPA	Environmental Protection Agency
EXPRES	Expert system for Pesticide Regulatory Evaluation and Simulation
GUS	Groundwater Ubiquity Score
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
K_{ow}	*n*-octenol-water constant
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
MOE	margin of exposure
MOS	margin of safety
NOAEL	no observed adverse effect level
PCP	pest control products
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
PRDD	Proposed Regulatory Decision Document
RAC	raw agricultural commodities
ROC	residue of concern
TSMP	Toxic Substances Management Policy
U.S.	United States
UV	ultraviolet

Appendix I Toxicological summary

METABOLISM

Absorption: Single or repeated doses of 5 mg/kg bw of RPA 400727 in rats were readily and extensively absorbed.

Distribution: The maximum plasma concentration was reached at 0.6 h (5 mg/kg bw) and 1.6–2 h (500 mg/kg bw) in both sexes. Tissue residues after each of the three protocols were low and not dose proportional; no indication of accumulation was observed. The highest residues were found in the liver, skin and fur (500 mg/kg bw) and in adrenals and plasma in males and adrenals and fat in females (5 mg/kg bw).

Excretion: Doses were rapidly and almost completely eliminated within 48 h. By day 7, 3–15% (males) and 5–32% (females) were excreted via the urine and 81–96% (males) and 65–96% (females) were excreted via the faeces. Terminal biological half-life was 95–118 h.

Metabolism: Doses were metabolized and subsequently excreted primarily in the faeces as unconjugated metabolites. The terminal biological half-life was 95–118 h. Repeated dosing over 14 days did not alter the pharmacokinetic profile of the compound. Differences in metabolism and excretion between males and females were minor and quantitative rather than qualitative. The major faecal metabolites were identified as RPA 405826 and RPA 406972 (5 mg/kg bw) and RPA 405826 (500 mg/kg bw). Urine from all three dose groups was found to contain up to 12 metabolites, 4 of which (RPA 406972, RPA 404766, RPA 406780 and RPA 406341) accounted for the bulk of the radiolabel. These were identified only as derivatives of the parent compound.

Study	Species (strain) and doses	LD_{50} (mg/kg bw) LC_{50} (mg/L)	Significant effects and comments
Acute studies: technical (RPA 400727)			
Oral	Rat (CD) 5/sex, at 2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** Decreased motor activity and ataxia in all animals
Dermal	Rat (CD) 5/sex at 2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** Dermal irritation noted at administration site
Inhalation	Rat (CD) 5/sex at 1.40 mg/L (maximum attainable concentration)	LC_{50} > 1.40	**Slight acute toxicity** Excessive salivation
Dermal irritation	Rabbit (NZW) 0.1-g dose unwashed: 3/sex;	MAS = 0	**Non-irritant**
Eye irritation	Rabbit (NZW) 6 males 0.1-g dose (1991) Rabbit (NZW) 6 females 0.1-g dose (1997)	MIS (1 h) = 4.7 MIS (1 h) = 2.7	**Minimal irritant** Iridial inflammation (2/6); conjunctival erythema (5/6) and erythema (2/6), resolved by 48 h **Minimal irritant** Conjunctival erythema and discharge (6/6), resolved by 24 h

Study	Species (strain) and doses	LD_{50} (mg/kg bw) LC_{50} (mg/L)	Significant effects and comments
Skin sensitization	Guinea pig (Dunkin Hartley (DH)) 10/sex **Buehler:** [Ind: 50% w/v a.i. (0.25 mL); challenge with 10 and 50% a.i. in propylene glycol] **GPMT:** (Ind. 0.1 mL of 5% w/v a.i. followed by 50% w/v propylene glycol; challenge with 10 and 50% a.i. in propylene glycol)	**Buehler:** No evidence of sensitization **GPMT:** Some slight erythema after induction; 50 and 10% a.i. groups showed no reaction after challenge	**Not a sensitizer**
Acute studies: Impurity (RPA 402570)			
Oral	Rat(CD) 5/sex, at 2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** No deaths; no clinical signs
Dermal	Rat (CD) 5/sex at 2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** No deaths or clinical signs, no signs of dermal irritation noted at administration site
Acute studies: Charter® EP			
Oral	Rat (Crl:CD® BR) 5/sex at 5000 mg/kg bw	LD_{50} > 5000 (males + females)	**Low acute toxicity** No deaths
Dermal	Rabbit (NZW) 5/sex at 2000 mg/kg bw	LD_{50} > 2000 (males + females)	**Low acute toxicity** No deaths; signs of minimal dermal irritation in all animals (erythema resolved by day 11; edema resolved by day 2)
Inhalation	Rat (Crl:CD® BR) at 3.25 mg/L	LC_{50} > 3.25 (males + females)	**Low acute toxicity** No deaths; decreased activity and piloerection resolved by day 2
Skin irritation	Rabbit (NZW) 5 males/1female, 0.5-mL dose	MIS = 2.0 (1 h) MAS = 0.6 (24, 48, 72 h)	**Slightly irritating** Observation of very slight erythema and edema in 6/6 rabbits with clearing by 72 h (all animals)
Eye irritation	Rabbit (NZW) 2 males/7 females, 0.1-mL dose <u>Unwashed group:</u> 1 male/5 females <u>Washed group</u>: 1 male/2 females	<u>Unwashed</u> MIS= 7.8 (1 h) MAS = 1.8 (24, 48, 72 h) <u>Washed</u> MIS= 10.0 (1 h) MAS = 1.1 (24, 48, 72 h)	**Minimally irritating** Iridial inflammation reversible by 24 h; minimal conjunctival irritation (erythema, chemosis), which was fully reversible within 7 days
Skin sensitization (Buehler method)	Guinea pig (DH derived), 5/sex, 0.3-mL dose; administered at 100% for induction and challenge		**Not a sensitizer**

SHORT TERM/SUBCHRONIC			
Study	**Species (strain) and doses**	**NOAEL/LOAEL (mg/kg bw/day)**	**Significant effects at different doses (mg/kg bw/day) and comments**
42-day dietary	Mouse (CD-1); 12/sex/group; 0, 10, 30, 100, 250 or 500 ppm (males: 0, 1.5, 4.3, 15.5, 36.9 or 73.1 mg/kg bw/day; females: 0, 2.0, 5.9, 19.1, 45.5 or 99.2 mg/kg bw/day).	NOAEL = 500 ppm (73.1 males/ 99.2 females) LOAEL not determined	**500 ppm:** increased liver weight (slight) and hepatocyte hypertrophy (males); considered as an adaptive response Note: supplementary study
42-day dietary	Mouse (CD-1); 12/sex/group; 0, 500, 1500, 5000, 15 000 or 50 000 ppm (males: 0, 77.7, 233, 851 or 3270 mg/kg bw/day; females:0, 98.8, 286, 982 or 4091 mg/kg bw/day) [Compound consumption (mg/kg bw/day) could not be determined for the 50 000 ppm group, since all animals died within the first week of the study.]	NOAEL = 1500 ppm (233 males/ 286 females) LOAEL = 5000 ppm (851 males/ 982 females)	**5000 ppm:** increased liver weight; liver histopatology [hepatocyte hypertrophy, fatty vacuolation, multiple nuclei and focal mineralization (males)] ≥**15 000 ppm:** decreased body weight gain and food intake; mortality and clinical signs (piloerection, pallor, hunched posture); bile duct proliferation (males), decreased uterus weight (no histopathology) **50 000 ppm:** mortality (100% by day 6)
13-week dietary	Mouse (CD-1); 12/sex/group; 0, 2500, 5000 or 8000 ppm (males: 0, 382.8, 807.6 or 1426.2 mg/kg bw/day; females: 0, 503.8, 969.2 or 1657.6 mg/kg bw/day)	NOAEL not determined LOAEL = 2500 ppm (382.8 males/ 503.8 females)	≥**2500 ppm:** decreased body weight gain and food efficiency; enlarged livers; increased liver weight; hepatocyte hypertrophy, hepatocytic fatty vacuolation and necrosis; bile plug formation (males), decreased uterus weight (no histopathology) ≥**5000 ppm:** increased hepatocyte mitotic activity; bile plug formation (females)

Study	Species (strain) and doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg bw/day) and comments
4-week dog (determination of maximum tolerated dose (MTD)	Dog (beagle), 1/sex **Group 1:** increasing doses of 10, 20, 40, 80, 160, 640 mg/kg bw/day; doses held for 3 days at each level, and 320 and 1000 mg/kg bw/day; doses held for 6 days **Group 2:** 1000 mg/kg bw/day for 3 days, untreated for 11 days followed by 14 days at 500 mg/kg bw/day **Group 3:** 300 mg/kg bw/day for 14 days (capsule)	MTD: 300 mg/kg bw/day	Group 1 ≥**40:** decreased body weight gain (male) ≥**80:** decreased body weight gain (female) **1000:** overt clinical signs (male) Group 2 **1000/500:** weight loss, increased liver weight, increased hepatic enzyme parameters, overt clinical signs of intoxication (ataxia, torpor, tremors, disorientation and convulsions); one male at 1000/500 mg/kg bw/day killed in extremis following the second dose Group 3 **300:** increased liver weight, increased hepatic enzyme parameters; clinical signs in dogs treated at 300 mg/kg bw/day cleared within the first few days of dosing
1-year dog	Dog (beagle) 4/sex 0, 2.5, 25 or 150 mg/kg bw/day (capsule)	NOAEL = 2.5 LOAEL = 25	≥**25:** decreased body weight gain (females), decreased albumin (males), increased ALP (females), vacuolation of adrenal cortical cells (zona fasciculata) (males/females) **150:** decreased body weight gain (males), clinical signs, decreased cholesterol (males/females), decreased albumin (males), increased ALP (males), lenticular cataracts (4/4 males and 3/4 females), increased absolute and relative testes weight, decreased absolute and relative prostate weight in males
SHORT TERM/SUBCHRONIC			
23-day dermal	Rat [Crl:CD (SD)BR Vaf Plus] 5/sex/group, 0, 100, 300 or 1000 mg/kg bw/day	NOAEL = 1000 LOAEL not determined	No systemic treatment-related effects at any dose level tested; dermal irritation was not observed at any dose level tested
14-day gavage; comparative study	Rat (Sprague-Dawley CD); 5/sex/group; RPA400727 (technical active) or RPA402570 (impurity of synthesis): 0, 10, 100 or 1000 mg/kg bw/day	NOAEL = 100 LOAEL = 1000 (for RPA400727 and RPA402570)	**1000 ppm:** RPA 400727 (technical active): increased liver weight and hepatocyte vacuolation (females); thickened glandular gastric (males) and forestomach (females) epithelium RPA 402570 (impurity): increased liver weight and hepatocyte vacuolation; hyperkeratosis and acanthosis in the forestomach (males)

Study	Species (strain) and doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg bw/day) and comments
4-week dietary	Rat (F-344); 5/sex/group; 0, 500, 1500, 5000, 15 000 or 50 000 ppm (males: 0, 50.1, 152.3, 513.2, 1494 or 4802 mg/kg bw/day; females: 0, 52.4, 151.3, 489.4, 1476 and 4945 mg/kg bw/day)	**Males:** NOAEL = 1500 ppm (152.3) LOAEL = 5000 ppm (513.2) **Females:** NOAEL = 5000 ppm (489.4) LOAEL = 15 000 ppm (1476)	≥**500 ppm:** decreased uterus weight (no histopathology) ≥**5000 ppm:** decreased body weight gain, food intake and food efficiency (males), decreased prostate weight (no histopathology) ≥**15 000 ppm:** decreased food efficiency; increased liver weight; hepatocyte vacuolation; necrosis (males); decreased uterus weight with reduced uterine endometrial stroma **50 000 ppm:** General clinical signs of toxicosis, decreased body weight gain(females), decreased serum glucose, ketonuria, hepatocyte hypertrophy; decreased prostate weight, decreased ovary weight (no histopathology)
13-week dietary	Rat (CD); 10/sex/group; 0, 25, 250, 12 500 and 25 000 ppm (males: 0, 2.0, 19.8, 1117.0 or 2309.3 mg/kg bw/day; females: 0, 2.2, 22.3, 1183.5 and 2368.8 mg/kg bw/day)	**Males:** NOAEL < 25 ppm (<2.0) LOAEL = 25 ppm (2.0) **Females:** NOAEL = 250 ppm (22.3) LOAEL=12500 ppm (1183.5)	≥**25 ppm:** adrenocortical fatty vacuolation (males) ≥**250 ppm:** hepatocyte hypertrophy (males) ≥**12 500 ppm:** generalized hair loss, decreased body weight gain, food intake and food efficiency; increased serum cholesterol (females), increased liver weight; hepatocyte hypertrophy (females), fatty vacuolation (females; degeneration of the adrenal zona reticularis (females); adrenocortical fatty vacuolation
CHRONIC TOXICITY/ONCOGENICITY			
78-week dietary	Mouse (CD-1) 68/sex/group 0, 15, 150 or 1500 ppm (males: 0, 1.8, 17.4 or 202.2 mg/kg bw/day; females: 0, 2.1, 20.1 or 209.5 mg/kg bw/day)	**Chronic effects:** NOAEL = 150 ppm (17.4 males/ 20.1females) LOAEL = 1500 ppm (202.2 males/ 209.5 females)	**1500 ppm:** increased liver weight, enlarged livers; hepatocyte hypertrophy (males) and fatty vacuolation; decreased body weight gain (females), decreased food efficiency (males), increased adrenal weight (males/females at interim sacrifice only; no histopathology) No treatment-related oncogenic effects at any dose level tested

Study	Species (strain) and doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg bw/day) and comments
100-week dietary	Rat (CD-1) 80/sex/group 0, 5, 25, 750 or 5000 ppm (males: 0, 0.2, 1.0, 29.4 or 203.6 mg/kg bw/day; females: 0, 0.3, 1.3, 38.3 or 286.6 mg/kg bw/day)	**Chronic effects** NOAEL = 750 ppm (29.4 males/ 38.3 females) LOAEL = 5000 ppm (203.6 males/ 286.6 females) **Oncogenicity** **Males:** NOAEL = 750 ppm (29.4) LOAEL = 5000 ppm (203.6) **Females:** NOAEL = 5000 ppm (286.6) LOAEL not determined	**5000 ppm:** decreased body weight gain and food efficiency (females), multinucleated cells in the adrenal (females), chronic inflamm of adrenal (females), hepatocyte fatty vacuolation (females), increased incidence of thyroid follicular cell adenomas (males)
REPRODUCTION/DEVELOPMENTAL TOXICITY			
Multi-generation	Rat (Crl:CD® BR), 2 generations, (1 litter/generation) 28/sex/dose 0, 5, 25, 750 or 5000 ppm via diet (males: 0, 0.3, 1.6, 49.4 or 307.2; females: 0, 0.4, 1.8, 54.7 or 386.6 mg/kg bw/day)	**Systemic toxicity:** NOAEL = 750 ppm (49.4 males/ 54.7 females) LOAEL = 5000 ppm (307.2 males/ 386.6 females) **Offspring toxicity:** NOAEL = 750 ppm (54.7) LOAEL = 5000 ppm (386.6) **Reproductive toxicity:** NOAEL = 750 ppm (54.7) LOAEL = 5000 ppm (386.6)	**Parents** **5000 ppm:** increased maternal deaths (F_0 females); decreased parental body weight decreased body weight gain, decreased food consumption (F_0 females, F_1 males + females), increased liver weight and liver pathology, decreased adrenal weight and adrenal pathology ($F_{0/1}$ females); adrenal pathology ($F_{0/1}$ females) **Offspring** **5000 ppm:** decreased $F_{1/2}$ pup body weight; decreased viability index $F_{1/2}$ pups **Reproductive parameters** **5000 ppm:** decreased fertility and mating indices F_1; increased gestation interval F_0, increased ovary weight and pathology (vacuolation) (F_1 females), increase in stillborn pups (F_0), decreased litter size (F_1), decreased live birth index $F_{1/2}$ pups

Study	Species (strain) and doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg bw/day) and comments
Teratogenicity	Rat (Crl:CD® BR) 25 females/dose 0, 40, 200 or 1000 mg/kg bw/day, by gavage (in methyl cellulose) on gestation days 6–15	**Maternal:** NOAEL =1000 (HDT) **Developmental:** NOAEL =1000 (HDT)	**Maternal toxicity** **1000:** marginal decreased body weight, decreased body weight gain, decreased feed consumption, not considered adverse **Developmental toxicity** **1000:** increased incidence of 14th rib pairs of ribs (variation not considered to be adverse) **Not teratogenic**
Teratogenicity	Rabbit (NZW) 20/dose 0, 5, 25, 50 or 75 mg/kg bw/day by gavage (in methyl cellulose) on gestation days 6–19	**Maternal:** NOAEL = 5 LOAEL = 25 **Developmental:** NOAEL = 5 LOAEL = 25	**Maternal toxicity** **≥25:** decreased body weight gain and food consumption; **≥50:** increased maternal deaths, increase respiration rate; **75:** slight increase in pre- and post-implantation loss **Fetal toxicity** **≥25:** increase elongation of acromion process **≥50:** increase in various skeletal abnormalities (increased incidence of delayed ossification of digits) **Not teratogenic**
NEUROTOXICITY			
Acute (range-finding and time-to-peak-effect)	Rat (Crl:CD® BR), 4/sex/dose 0, 50, 1000 or 2000 mg/kg bw	Doses for definitive acute study determined to be 80, 400 and 2000 mg/kg bw	Time-to-peak-effect is 3 h post-dosing; dose-related increase in motor activity greatest at 3 h post-dose; no effects on FOB tests
Acute	Rat (Crl:CD® BR), 10/sex/dose, via single gavage dose of 0, 80, 400 or 2000 mg/kg bw; observed for 15 or 16 days post-dose	**Neurotoxicity:** NOAEL = 2000 mg/kg bw (the highest dose tested)	No treatment related effects on mortality, clinical signs, body weight, brain size or gross/histologic pathology or neuropathology; no effects on functional observation battery
Subchronic	Rat (Crl:CD® BR), 10/sex/dose 0, 500, 2500 or 10000 ppm (males: 0, 32.5, 170.0 or 695.1 mg/kg bw/day; females: 0, 38.5, 199.4 or 820.3 mg/kg bw/day) via diet for 90 days	**Neurotoxicity:** NOAEL > 695 males/820 females	No mortalities of clinical signs of toxicity; no effects on functional observation battery nor neuropathology at highest dose tested.

Study	Species (strain) and doses	NOAEL/LOAEL (mg/kg bw/day)	Significant effects at different doses (mg/kg bw/day) and comments
GENOTOXICITY			
Study	**Species and strain or cell type**	**Doses employed**	**Significant effects and comments**
Technical active (RPA 400727)			
Reverse mutation	*S. typhimurium*, ±S9	25, 79, 250, 790, 2500 μg/plate	Negative
Gene mutation	Chinese hamster V79 cells ±S9	62.5, 125, 250, 500, 1000 μg/mL	Negative
Chromosome aberration	Human lymphocytes ±S9	+ S9: 125, 250, 500 μg/mL – S9: 10, 20, 40, 50, 60 μg/mL	Negative Negative
Micronucleus test	Mouse	25, 125, 625 mg/kg bw	Negative
Unscheduled DNA synthesis	Rat	7.8, 15.6, 31.3, 62.5, 125 μg/mL	Negative
Impurity (RPA 402570)			
Reverse mutation	*S. typhimurium*, ±S9	100, 250, 500, 1000, 2500 μg/plate	Negative

Appendix II Summary of food residue chemistry studies

PLANT METABOLISM

Triticonazole readily metabolized in winter and spring wheat and barley. Metabolic profile in plant species suggests hydroxylation as the major pathway.

ROC defined as the parent triticonazole.

	Winter barley						Spring barley			
	Grain (TRR = 0.05 ppm)		Chaff (TRR = 1.07 ppm)		Straw (TRR = 1.69 ppm)		Chaff (TRR = 1.43 ppm)		Straw (TRR = 2.35 ppm)	
Residue	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	% TRR
Triticonazole	0	33.2	0.07	6.4	0.52	30.6	0.08	6	0.66	28
RPA 404766	nd	nd	0.14*	13*	0.1	5	0.12*	9*	0.17	7
RPA 406780	nd	nd			0	0.6			nd	nd
RPA 404886	nd	nd	0.27	25.3	0.1	5.4	0.14	10	0.35	15
RPA 406341	0	33.2	0.08	7.6	0.11	6.5	nd	nd	nd	nd
RPA 406203	nd	nd	nd	nd	0	1.3	nd	nd	nd	nd
Metabolite A	nd	nd	0.33	31.3	0.19	10.8	0.74	51	0.49	21
Unidentified metabolites	0	22.6	0.03	3	0.28	16.3	0.14	9	0.12	5
Total identified	0	66.4	0.56	52.3	0.83	49.4	0.34	25	1.18	50
Total unidentified	0	22.6	0.36	34.3	0.47	26.9	0.88	60	0.61	26
Total extractable	0	89	0.92	86.6	1.3	76.3	1.22	85	1.79	76
Total unextractable	0	11	0.15	13.5	0.4	23.7	0.21	15	0.56	24
Total	0.1	100	1.07	100	1.7	100	1.43	100	2.35	100
Accountability	100	100	100	100	100	100	100	100	100	100

Residue	Winter wheat						Spring wheat			
	Grain (TRR = 0.01 ppm)		Chaff (TRR = 0.15 ppm)		Straw (TRR = 2.23 ppm)		Chaff (TRR = 1.05 ppm)		Straw (TRR = 2.08 ppm)	
	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR
Triticonazole	na	na	0.03	17.7	0.63	28.4	0.28	27	0.37	18
RPA 404766	na	na	nd*	nd*	0.15*	6.7*	0.26	25	0.21	10
RPA 406780	na	na					nd	nd	nd	nd
RPA 404886	na	na	0.04	26.9	0.4	17	0.26	24	0.27	13
RPA 406341	na	na	0.01	8.7	0.27	12.1	nd	nd	nd	nd
RPA 406203	na	na	nd	nd	nd	nd	nd	nd	nd	nd
Metabolite A	na	na	0.04	25.3	0.21	9.3	nd	0	0.37	18
Unidentified metabolites	na	na	0.01	7.9	0	1.2	nd	0	0	1
Total identified	na	na	0.08	53.3	1.45	64.2	0.8	76	0.85	41
Total unidentified	na	na	0.05	33.2	0.24	10.5	nd	0	0.4	19
Total extractable	na	na	0.13	86.5	1.69	74.7	0.8	76	1.25	60
Total unextractable	na	na	0.02	13.5	0.54	25.3	0.27	26	0.83	40
Total	na	na	0.15	100	2.23	100	1.07	102	2.08	100
Accountability	na	na	100	100	100	100	102	102	100	100

*Values represents combined result for both RPA 404766 and RPA 406780, since the two residues could not be separated in the experiment.
na: not available; nd: not determined.

CONFINED CROP ROTATION STUDIES
Soil incorporation of [phenyl-^{14}C]triticonazole at rate of 285.9 g a.i./ha.

Uptake of triticonazole into RACs of three representative crops was low and appeared to decline with time. Triticonazole was the predominant extractable residue. Therefore, application of triticonazole at normal seed dressing rate would result in minimal uptake in rotational, secondary crops.

Crop	Triticonazole equivalents (ppm)		
	30-day tilling	149-day tilling	366-day tilling
Radish bulbs	0.022	0.0049	0.0077
Radish leaves	0.077	0.032	0.022
Lettuce leaves	0.048	0.015	0.033
Wheat grain	0.0029	0.0037	0.004
Wheat chaff	0.03	0.02	0.058
Wheat straw	0.16	0.17	0.11

ANIMAL METABOLISM

In dairy cattle and poultry metabolism, triticonazole is fairly well and rapidly absorbed and eliminated (mainly via faeces) with minimal tissue accumulation. Metabolism was rapid with only trace amounts of parent compound recovered unchanged from the faeces.

Poultry:

Parent and RPA 406972 acid metabolite were predominant residue in eggs and poultry liver, respectively. The nature of the residues in skin and fat were too low for metabolite identification/characterization.

Dairy cattle:

The hydroxylated metabolites RPA 404766, RPA 404886 and RPA 406780 were the predominant residues in kidney and liver. The total radioactive residues in milk, muscle and fat were too low for metabolite identification/characterization. Metabolic profile in animal species suggests hydroxylation as the major pathway.

ROC defined as the parent triticonazole.

	Dairy cattle				Poultry			
	Low dose		High dose		Low dose		High dose	
Matrix	% Dose	ppm	% Dose	ppm	% Dose	ppm	% Dose	ppm
Tissues	0.262		0.237		0.06		0.03	
Kidney		0.003		0.035	—	—	—	—
Liver		0.021		0.238		0.035		0.155
Muscle		<0.004		<0.004		<0.003		0.003
Fat		<0.004		<0.004		<0.003		0.036
Milk	<0.001		0.005					
Egg white					0.18	0.004	0.16	0.1
Egg yolk					0.18	0.025	0.12	0.19
Excreta	81.18		83.97		107.29		85.52	

FREEZER STORAGE STABILITY TESTS, PLANT MATRICES: Stability of triticonazole residues at -20°C (0, 3, 6, 12 months).

Triticonazole residues in maize and winter wheat grain and winter wheat straw were stable for 12 months.

	Matrix		
	Maize grain	**Winter wheat grain**	**Winter wheat straw**
Spiking level (ppm)	0.01	0.01	0.05
Recovery (%)			
0 months storage	112±1 (n = 3)	110±3 (n = 3)	94±14 (n = 3)
3 months storage	100±2 (n = 3)	93±2 (n = 3)	71±4 (n = 3)
6 months storage	89±1 (n = 3)	97±22 (n = 3)	101±2 (n = 3)
12 months storage	100±7 (n = 3)	108±8 (n = 3)	120±10 (n = 3)

FREEZER STORAGE STABILITY TESTS: ANIMAL MATRICES

Not available

SUPERVISED RESIDUE TRIALS ON CEREALS

Commodity/portion analysed	Formulation	Application		Post-emergence interval (days)	Residues (ppm)
		Total rate (g a.i./00 kg seed)	% gap		
1995 Supervised residue trials: wheat and barley					
Forage	Flowable formulation (200 g a.i./L)	10	400	30	<0.05
Grain	Flowable formulation (200 g a.i./L)	10	400	77–116	<0.01
Straw	Flowable formulation (200 g a.i./L)	10	400	77–116	<0.05
1996 Supervised residue trials: wheat, barley and oats					
Forage	Flowable formulation (25 g a.i./L)	35	1400	30	<0.05
Grain	Flowable formulation (25 g a.i./L)	35	1400	77–116	<0.01
Straw	Flowable formulation (25 g a.i./L)	35	1400	77–116	<0.05

PROCESSING STUDIES

Triticonazole residues in cereal grains were <0.01 ppm when seeds treated 14× proposed Canadian rate (2.5 g a.i./ha).

No processing studies required.

CATTLE AND POULTRY FEEDING STUDIES

The maximum anticipated dietary burdens of triticonazole to beef, dairy cattle and poultry are 0.2, 0.4 and 0.03 ppm, respectively, based on diets consisting of forage, straw and grain and the recommended MRLs of 0.05 ppm (forage and straw) and 0.01 ppm (grain). Based on the supervised field trials, residues of triticonazole in forage, grain and straw did not exceed the method LOQs (forage and straw, 0.05 ppm; grain, 0.01 ppm), when treated at rates of up to 14× the proposed Canadian maximum seasonal application rate. The dairy cattle and poultry metabolism studies demonstrated that there were no residues of triticonazole or any compound of toxicological interest detected at levels greater than 0.01 ppm in the milk and 0.05 ppm in meat and meat by-products, when administered a diet representing 5–333× the theoretical maximum dietary burden. Since it appears unlikely that any residues of triticonazole will bioaccumulate in milk, eggs, beef and poultry meat and meat by-products, no feeding studies were required.

PROPOSED MRLs

Crop	Proposed Canadian MRLs (ppm)
Wheat, barley and oat grain	0.01
Milk	0.01
Eggs	0.05
Poultry meat and meat by-products	0.05
Meat and meat by-products of cattle, goat, hogs, horses and sheep	0.05

CHRONIC DIETARY RISK ASSESSMENT using DEEM Software based on the 1994–1996 Continuing Survey of Food Intake by Individuals (ADI = 0.008 mg/kg bw; Tier I: using the proposed MRLs)

	All U.S. population	All infants (<1 year)	Children (1–6 years)	Children (7–12 years)	Children (13–19 years)	Children (20+ years)	Seniors 55+ years
% of ADI	3	2	7	4	3	2	2

ACUTE DIETARY RISK ASSESSMENT using DEEM software based on the 1994–1996 Continuing Survey of Food Intake by Individuals (ARfD = 0.017 mg/kg bw for females 13+)

95th percentile	Females 13+, pregnant and nursing
% of ARfD	2

Appendix III

Table 1 Summary of transformation and mobility data for triticonazole

Study	Value	Interpretation
Hydrolysis	No hydrolysis after 30 days	Not a route of dissipation in the environment
Phototransformation	No data	Phototransformation on soil will not likely be a route of dissipation in the environment based on UV/visible absorption spectrum
Aerobic biotransformation	DT_{50}: 145–554 days	Moderately persistent to persistent in aerobic soil
Adsorption/desorption	$K_{d\text{-}ads}$: 1.7–31.7 $K_{oc\text{-}ads}$: 184–563	Low to moderate potential for mobility
Unaged and aged soil column leaching	89% remained in the top 18 cm of soil; 70 and 27% found in leachates in unaged and aged sand soil, respectively	Low to moderate potential for leaching with the exception of sandy soil, where it is high; 95% of the applied compound remained as parent; transformation products were RPA 404766 and RPA 406341; transformation products are more polar and have higher mobility in soil

Table 2 Summary of transformation products formed in terrestrial fate studies

Study	Major transformation products (% of applied)	Minor transformation products (% of applied)
Aerobic biotransformation	RPA 406780 (Met 1) 9.9% RPA 406341 (Met 3) 15.3% ; IUPAC: (1R,3R,E)-2-(4-chlorobenzylidene)-5,5-dimethyl-1-((1H)-1,2,4-triazol-1-ylmethyl)-cyclopentan-1,3-diol) RPA 407922 (Met 6) 11.5% RPA 404766, 9.5% ; IUPAC: (E)-2-(4-chlorobenzylidene)-5,5-dimethyl-1-((1H)-1,2,4-triazol-1-ylmethyl)-cyclopentan-1,3-diol)	RPA 40886 (Met 2) Unidentified transformation products: Met 4, Met 5, Met 7, Met 8, Met 9, Met 10 and Met 11 With the exception of Met 5, which is reported as 7%, the other minor transformation products were not seen consistently and reached a maximum value of 2%.
Adsorption/ desorption	Characterization of transformation products is not a part of these studies	
Unaged and aged soil column leaching	RPA 404766, IUPAC: (E)-2-(4-chlorobenzylidene)-5,5-dimethyl-1-((1H)-1,2,4-triazol-1-ylmethyl)-cyclopentan-1,3-diol) (percentage was not specified) and RPA 406341, IUPAC: (1R,3R,E)-2-(4-chlorobenzylidene)-5,5-dimethyl-1-((1H)-1,2,4-triazol-1-ylmethyl)-cyclopentan-1,3-diol) (percentage was not specified)	None
Canadian field dissipation	Studies were not acceptable	
European field dissipation	RPA 406341, IUPAC: (1R,3R,E)-2-(4-chlorobenzylidene)-5,5-dimethyl-1-((1H)-1,2,4-triazol-1-ylmethyl)-cyclopentan-1,3-diol) 11%	None

Table 3 Summary of terrestrial toxicity endpoints

Toxicity	Organism	NOEC/NOEL (mg a.i./kg bw or diet)	LD_{50}/LC_{50} (mg a.i./kg bw or diet)	Interpretation
Acute	Bobwhite quail	2000	>2000	Practically non-toxic
	Mallard duck	1000	>2000	Practically non-toxic
	Grey partridge	nd	>2000	Practically non-toxic
	Red-legged partridge	nd	>2000	Practically non-toxic
	Pigeon	nd	>2000	Practically non-toxic
	Ring-necked pheasant	nd	>2000	Practically non-toxic
	Rat	nd	>2000	Practically non-toxic
Dietary	Bobwhite quail	1300	>5200	Practically non-toxic
	Mallard duck	1300	>5200	Practically non-toxic
	Mouse (42-day study)	1500		
	Rat (4-week study)	1500		
	Rat (13-week study)	250 (females) No NOEL (males)		
Reproduction	Bobwhite quail	250	>1000	Practically non-toxic
	Rat	49.4		

nd: not determined